Annual Surveillance Summary: Vancomycin-Resistant Enterococci (VRE) Infections in the Military Health System (MHS), 2015

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Abstract

This report provides an annual update for calendar year (CY) 2015 of vancomycin-resistant Enterococci (VRE) infection burden among Military Health System (MHS) beneficiaries from previously reported retrospective data. The methods assess the demographics, clinical characteristics, prescription practices, and antibiotic susceptibility patterns for VRE infections across the Department of Defense (DOD) and Department of the Navy (DON) active duty (AD) service members with deployment-related infections. In 2015, the annual VRE incidence rate (IR) for all MHS beneficiaries was 1.60 per 100,000 persons per year, reflecting a 19.4% increase compared to the weighted historic IR. United States (US) West and South regions accounted for the highest IRs, and healthcare-associated (HA) cases were the largest proportion of all infections identified. A substantial percentage of HA cases were classified as community-onset (CO) and multi-drug resistant organism (MDRO) admission metrics demonstrated a higher magnitude of VRE was imported into the MHS. This indicates a need to evaluate the potential for community transmission of VRE. Treatment for VRE infections among DOD beneficiaries primarily included daptomycin and linezolid, which remained effective throughout 2015. These findings warrant continued surveillance to understand the evolving impact of VRE within the MHS.

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Background

Enterococci are normal inhabitants of the human gut and typically do not cause infection unless the host has a suppressed or compromised immune system.[1] Although multiple *Enterococcus* species have been identified, two are responsible for the majority of human infections, *Enterococcus faecium* or *E. faecalis*. Almost all nosocomial infections are associated with one of these species and arise in the urinary tract or the intra-abdominal cavity.[2,3] In the 1980's, antibiotic resistance to beta-lactam antibiotics and high concentrations of aminoglycosides emerged for enterococci, and vancomycin represented the last effective antibiotic for drug-resistant *E. faecium*.[3] In 1988, the first VRE outbreak was reported in Europe. Within a decade of identification, the emerging pattern of antimicrobial resistance to vancomycin among enterococci became a worldwide trend.[3,4,5]

During the early 1990's, enterococci became the second most reported nosocomial infection in the United States (US).[6] Longitudinal surveillance data collected by the National Nosocomial Infection Surveillance System of the Centers for Disease Control and Prevention (CDC) demonstrated a clear emergence of VRE within US hospitals. In 1989, almost all enterococci blood isolates were susceptible to vancomycin, but the proportion of resistant strains increased to 12.8% in 1995 and to 25.9% by 2000.[7] Furthermore, in 1999 the SENTRY Antimicrobial Surveillance Program identified 17% of US enterococci isolates as vancomycin-resistant strains, significantly higher than those from the rest of the world.[5] Experts hypothesize this nosocomial spread of resistant genes developed in the US due to selective pressure caused by increased use of vancomycin for another multi-drug resistant organism (MDRO), methicillin-resistant *Staphylococcus aureus* (MRSA), as well as the common use of prophylactic vancomycin for surgical and indwelling catheter patients.[8]

Between 1998 and 1999, the SENTRY Antimicrobial Surveillance Program reported a decline in VRE across all regions in the US.[5] Researchers noted this decrease could be due in part to the implementation of recommendations established by the Hospital Infection Control Practices Advisory Committee (HICPAC).[5,9] However, current trends demonstrate that VRE infections are rising. One US study reported hospitalizations due to VRE infections increased from 3.2 per 10,000 hospitalizations to 6.5 per 10,000 total hospitalizations from 2003-2006.[10] Some European countries have also documented increasing rates of VRE infections, with vancomycin resistance reportedly as high as 28.0% among *E. faecium* isolates.[11] Experts believe that the continued, widespread use of vancomycin to treat MRSA is an important reason behind the increasing trend of VRE infections in the US.[12]

VRE infections have a tendency to occur in seriously ill, hospitalized patients, especially among patients with prolonged hospital stays and patients who recently received organ transplants.[2] Many factors may predispose a person to infection with VRE, but colonization precedes most infections.[13] In the US, nosocomial spread of VRE is characterized by direct person-to-person contact, including carriage on the hands of healthcare personnel, contaminated environmental surfaces, or contaminated patient care equipment. Vancomycin use likely predisposes patients to colonization and infection by inhibiting the growth of the normal Gram-positive intestinal flora and providing a selective advantage for VRE that may be present in small numbers in the

individual's bowel.[2] Furthermore, research demonstrates interhospital diversity among VRE isolates, strongly suggesting transmission between different medical center settings.[14] HICPAC recommends several actions to control VRE transmission in hospitals, including the prudent use of vancomycin, education of hospital staff, early detection, and prompt reporting of resistant strains.[9] Additionally, active surveillance of high-risk patients has been cited as a pertinent control measure in healthcare settings; one study demonstrated active surveillance with contact precautions prevented VRE infections in an intensive care unit (ICU) where 100% of the patients were colonized with VRE.[15]

In Europe, VRE are commonly characterized as community-acquired infections as opposed to hospital-associated infections (HAIs).[3] While hospital outbreaks for VRE have been reported across Europe, the overall proportions of vancomycin resistance isolated from nosocomial enterococci infections are low.[3,16] Several studies confirm colonization with VRE in healthy people and farm animals throughout Europe, and the causal relationship between an animal reservoir and colonization in humans is supported by growing circumstantial evidence.[3] The widespread use of avoparcin, a glycopeptide antimicrobial drug similar to vancomycin, is commonly cited as an important element to community transmission of VRE in Europe due to its use as a growth promoter in food-producing animals. Although avoparcin has never been approved for use in the US, experts caution that further studies of community VRE transmission are urgently needed.[17]

Treatment for enterococci infections normally includes an aminoglycoside plus another cell-wall active agent (β-lactam antibiotic). This is problematic for VRE infections, however, as they are often resistant to many or all of these antibiotics, leaving few treatment options.[4] For patients allergic to penicillin or who have ampicillin/penicillin-resistant strains, clinicians highly recommend vancomycin used in combination with other antibiotics, including aminoglycosides.[2] Quinupristin/dalfopristin was the first antibiotic developed for VRE. This antibiotic is only meant for treatment of *E. faecium*, as other *Enterococcus* isolates are intrinsically resistant to it. However, quinupristin/dalfopristin has not been widely used since 2001, as research has associated it with debilitating adverse events.[18] Linezolid, an oxazolidinone developed in 2000, is another relatively new first line antibiotic and is effective against *E. faecium* and several other *Enterococcus* species. Some resistance has already been reported for linezolid.[18] Resistance has also been documented with daptomycin, developed in 2003, which is another treatment option for Gram-positive bacterial infections.[18] Fluoroquinolones are not highly recommended to treat VRE infections; there are other classes of antibiotics more effective. However, fluoroquinolones are quite effective in the treatment of UTIs.[2]

This analysis presents an annual update for calendar year (CY) 2015 of VRE infection burden among Military Health System (MHS) beneficiaries from previously reported retrospective data. This report describes the demographics, clinical characteristics, prescription practices, and antibiotic susceptibility patterns for VRE infections among MHS beneficiaries, as well as Department of the Navy (DON) active duty (AD) service members with deployment-related infections.

Methods

The EpiData Center (EDC) at the Navy and Marine Corps Public Health Center (NMCPHC) conducted retrospective surveillance of VRE infection in the MHS in CY 2015 (01 January 2015 to 31 December 2015). Health Level 7 (HL7)-formatted Composite Health Care System (CHCS) microbiology data was used to identify positive *Enterococcus* laboratory results; any *Enterococcus* species laboratory result resistant to vancomycin was considered a VRE infection. BacLink and WHONET software programs, which were developed by the World Health Organization (WHO) to aid in the identification and analysis of MDROs, were used to identify VRE isolates and organize antibiotic susceptibilities within microbiology records.[19] A unique VRE infection was defined as the first positive VRE laboratory result per person per 30 days. Incidence represented the first unique infection per person per calendar year and prevalence was defined as all unique VRE infections.

Demographic Classification

Demographic information for each incident infection was described using data within the HL7-formatted CHCS microbiology record and infections were classified according to the patient's gender, age, sponsor service (Air Force, Army, Marine Corps, or Navy), duty status (Active Duty, Retired, Family Member, or Other), and region of the facility where the specimen was collected. The Active Duty category included both active duty and recruit personnel, defined by the beneficiary type codes of 11 and 13, respectively.

VRE incidence rates and prevalence infections were aggregated into six spatial regions and visualized as maps created in ESRI ArcGIS software (version 10.2.2). Organisms identified in each region may act as a reservoir within that region and contribute to the burden of exposure. Geographic regions were assessed within the continental United States (CONUS) and outside the CONUS (OCONUS), with the spatial regions identified as follows:

- **Northeast**: Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, New York, Pennsylvania, New Jersey.
- **Midwest**: Michigan, Wisconsin, Minnesota, Ohio, Indiana, Illinois, Iowa, Missouri, Kansas, Nebraska, North Dakota, South Dakota.
- **West**: California, Oregon, Washington, Idaho, Montana, Wyoming, Colorado, New Mexico, Arizona, Utah, Nevada, Alaska, Hawaii.
- **South**: Texas, Oklahoma, Arkansas, Louisiana, Mississippi, Alabama, Tennessee, Kentucky.
- **South Atlantic**: Delaware, Maryland, District of Columbia, Virginia, West Virginia, North Carolina, South Carolina, Georgia, Florida.
- **OCONUS**: All US territories and non-US countries.[20]

Clinical Characteristics Classification

Clinical characteristics were described for prevalent infections using information within the HL7-formatted CHCS microbiology record. Specimens were classified as inpatient or outpatient based on the Medical Expense and Performance Reporting System (MEPRS) codes of the location where the specimen was collected. A MEPRS code of A indicated specimen collection in the inpatient setting. All other MEPRS codes were considered outpatient encounters.

Infections were classified into invasive and non-invasive categories using the specimen source or body site variables in the HL7-formatted CHCS microbiology record. The terms used to group the data into these categories are described in Table 1. In addition, infections were further categorized based on body collection sites specific to the organism of interest (e.g., urine, respiratory, bloodstream) to provide enhanced granularity to the source of infection. Clinical characteristics were presented as a proportion of all infections within the population meeting the definition criteria.

Table 1. Invasive and Non-Invasive Infection Classification for VRE Infections Accessing the MHS

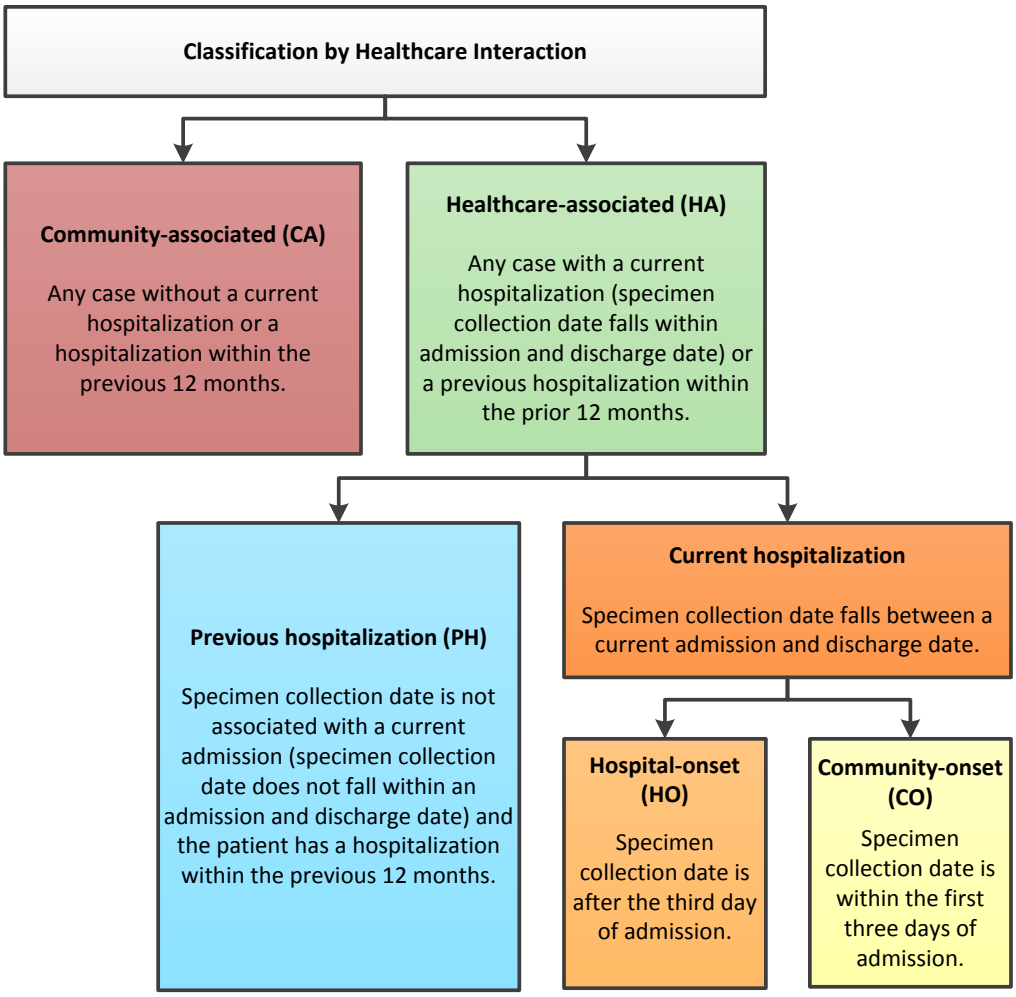
Infection Classification	If Body Site or Specimen Source Sample Taken From:
Invasive Infections	Blood, bone, cerebrospinal fluid, peritoneal fluid, pleural fluid, or synovial fluid
Other Non-Invasive Infections	Abscess, aspirate, body fluid, boil, bursa, carbuncle, cellulitis, cyst, discharge, drainage, exudate, eye, genital, lesion, pus, pustule, respiratory, skin, sputum, stool, swab, throat, tissue, urine, or wound

Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Epidemiologic Infection Classification

To evaluate all laboratory-confirmed VRE infections for recent contact with the healthcare system, VRE prevalence infections were matched to the Standard Inpatient Data Record (SIDR) to determine epidemiologic infection classification. Records were categorized as either community-associated (CA) or healthcare-associated (HA). CA cases were defined as patients without a current hospitalization nor a hospitalization in the previous 12 months. HA cases were defined as patients who were hospitalized at the time of infection (currently hospitalized) or who had a hospitalization within the previous 12 months. Current hospitalizations were further categorized as a hospital-onset (HO) case or a community-onset (CO) case. HO cases were defined as patients with a VRE organism identified after the third day of the current admission. CO cases were identified as patients with a specimen collected within the first three days of the current admission yielding a VRE organism, indicating the patient likely acquired the organism within the community and arrived at the treating facility with it.[21] Figure 1 presents the definitions for epidemiologic infection classifications.

Figure 1. Epidemiologic Infection Classifications[a]



[a]Cohen A, Calfee D, Fridkin SK, et al. Recommendations for metrics for multidrug-resistant organisms in healthcare settings: SHEA/HICPAC position paper. *Infect Cont Hosp Ep*. 2008;29(10):901-913.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Exposure Burden Metrics

Only the first unique MDRO infection per patient per admission was used to analyze exposure burden metrics in the MHS. Admission prevalence estimated the exposure of infection at the time of admission (importation of MDROs into the MHS), which included MDROs isolated from samples collected up to and including the third day of admission, as well as samples that tested positive for infection in the prior calendar year. Overall prevalence included all individuals with an MDRO infection identified from a sample collected at any point during the admission, or samples that tested positive for infection in the prior calendar year. Admitted patients with a history of colonization or infection were identified by searching prevalence infection MDROs

from the prior calendar year to determine a history of infection. These beneficiaries were counted in both the admission and overall prevalence populations as they contributed to the colonization pressure and exposure burden for those not already colonized or infected in both populations.[21] The historical review of data is included to show a reservoir of antimicrobial resistance and pressure among VRE infections. Regional rates of exposure burden were calculated as the rate of exposure (admission or overall prevalence) per 1,000 inpatient admissions per region per year.

Pharmacy Transactions

To analyze antimicrobial prescription practices in the MHS, the HL7-formatted microbiology VRE prevalence infections were matched to pharmacy data to identify antibiotic prescriptions associated with VRE infections in all pharmacy databases (outpatient oral (OP), inpatient oral (unit dose, or UD), and inpatient and outpatient intravenous (IV)). Prescriptions were considered to be associated with a VRE infection if the transaction date in the pharmacy record occurred either seven days before or after the date the specimen was certified in the laboratory data. All pharmacy transactions, regardless of database source (UD, IV, OP), were evaluated as one data source. Cancelled prescriptions or those with zero or null filled prescriptions were removed prior to analysis. A unique antibiotic prescription was defined as the first dispensed prescription for an antibiotic per prevalence infection. Antimicrobials recommended for treatment of VRE infections according to the Johns Hopkins Antibiotic Guide were retained for analysis.[22]

Antimicrobial Resistance Classification

To evaluate changes in antimicrobial susceptibility for VRE infections, an antibiogram was created using antibiotic susceptibility results from the microbiology record according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.[23] The antibiogram includes the first isolate per person per organism per year from 2010 to 2015. The Cochran-Armitage trend test was used to assess patterns in susceptibility across years. Trend direction for a single antibiotic over time was established using the two-tailed P-value; an increase in susceptibility was denoted by a green upward arrow and a decrease in susceptibility was denoted by a blue downward arrow. A statistically significant trend was established using a P-value $\leq .05$.

Special Populations

VRE infections identified among DON active duty personnel were matched to the Defense Manpower Data Center (DMDC) Contingency Tracking System (CTS) to explore deployment-related infections occurring on or between the start and end dates of the deployment plus 30 days. Thirty days post-end of deployment was used to ensure all VRE infections related to the deployment were included. Records with no deployment end date (i.e., service member remains deployed) were also included provided that the infection occurred in the analysis year (2015) and the start date of deployment was within 180 days of the specimen certification date.

Statistical Analysis

The MHS Data Mart (M2) was used to obtain counts of TRICARE eligible MHS beneficiaries for denominators. The annual incidence rate was defined as the count of all incident infections per year divided by the corresponding annual M2 eligible beneficiary count (represented by the

count in July) per year. A weighted average of incidence rates by month for the three years prior to the current analysis year (weighted historic monthly baseline) was used to assess the seasonal component of VRE infections in 2015. One and two standard deviations, both above and below the weighted historic monthly baseline, were used to indicate statistically significant changes in incidence rates of VRE infections in the analysis year.

All incidence rates are presented as an estimated rate per 100,000 persons per year. Due to the transient nature of the military beneficiary population and an inability to account for the proportion of the beneficiary population that receives medical care outside of the MHS, estimated rates are used for comparison of rates from year to year. A historical baseline was created using the weighted average of the immediately preceding three years. The historical baseline of the incidence rate serves as a clinical reference for the 2015 incidence rate. Two standard deviations on either side of the baseline were calculated to assess variation in incidence rate in the three years prior to the current evaluation period. Two standard deviations provide the upper and lower bounds (approximately 95%) for assessing whether the observed occurrence was likely due to change, and for consideration of clinically significant trends.

Results

Section A – Descriptive Epidemiology

Incidence of VRE

In 2015, the annual VRE incidence rate (IR) for all MHS beneficiaries was 1.60 per 100,000 persons per year, reflecting an incidence that is 19.4% above the weighted historic incidence rate; this increase remained within two standard deviations of the weighted historic incidence rate. In 2015, beneficiaries in the Air Force (1.56 per 100,000 persons) and Navy (1.42 per 100,000 persons) represented the highest rates by service. With the exception of the Navy, incidence rates were above the weighted historic incidence rate across all services; however, all services were within two standard deviations of the weighted historic IR. Assessment of incidence rates within DOD active duty personnel exhibited rates lower than any other beneficiary population, at 0.44 per 100,000 persons. While the incidence among active duty personnel increased by 9.1% above the weighted historic incidence rate, this trend did not exceed two standard deviations (Table 2).

Table 2. Incidence Rate (IR) for VRE Infections in the MHS, CY 2015

Population	2015 IR	Weighted Historic[a] IR 2012 - 2014	Two Standard Deviations: Weighted Historic[a] IR	2015	
				Direction	Percent Change[b]
MHS Beneficiaries	1.60	1.34	0.32	↑	19.4%
Air Force	1.56	1.10	0.54	↑	41.8%
Army	1.00	0.91	0.32	↑	9.9%
Marine Corps	0.68	0.67	0.02	↑	1.5%
Navy	1.42	1.58	0.84	↓	10.1%
DOD Active Duty	0.44	0.40	0.14	↑	9.1%

Rates are presented as the rate per 100,000 persons per year.
A green arrow indicates an increasing percent change and a blue arrow indicates a decreasing percent change.
[a] Historic IR reflects the weighted average of the three years prior to the analysis year.
[b] This reflects the percent change from the weighted historic IR to the IR of the current analysis year.
Data Source: NMCPHC HL7-formatted CHCS microbiology and MHS M2 databases.
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Demographic Distribution of VRE

In 2015, there were 151 incident infections of VRE identified among all MHS beneficiaries accessing care at a military treatment facility (MTF). Incidence rates among males (1.96 per 100,000 persons) exceeded females (1.23 per 100,000 persons). Burden increased with age, where beneficiaries 65 years and older experienced highest rates (4.75 per 100,000 persons). By beneficiary type, retirees had the highest incidence rates (2.35 per 100,000 persons), whereas family members (0.89 per 100,000 persons) and active duty personnel (0.44 per 100,000 persons) had the lowest (Table 3). Individuals with an 'other' beneficiary type (n=45) include persons who are not classified as active duty, retired, or family members; the majority were either 45-64 years old (n=10) or 65+ years old (n=29), had a service category of 'other' (n=39), or a patient category code indicating 'other, not classified elsewhere' (n=39) (data not shown).

Table 3. Demographic Characteristics of VRE Infections in the MHS, CY 2015

	N = 151	
	Count	**Rate**
Gender		
Female	57	1.23
Male	94	1.96
Age Group (in Years)		
0-17	2	--
18-24	2	--
25-34	5	--
35-44	5	--
45-64	33	1.58
65+	104	4.75
Beneficiary Type		
Active Duty	6	--
Family Members	49	0.89
Retired	51	2.35
Other[a]	45	--

Rates are presented as the rate per 100,000 persons per year.
Rates are not provided when the count is less than or equal to 10.
[a] Rate is not reported due to variation in the population denominator.
Data Source: NMCPHC HL7-formatted CHCS microbiology database.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Seasonality

Throughout 2015, VRE monthly incidence rates were variable, trending above and below two standard deviations of the MHS weighted historic monthly baseline; however, these highly variable trends may be explained by the overall low frequency of infections identified during the year (n=151), thus translating to even lower monthly frequencies (range: n=4 to 18 incident infections per month; median: n=14 incident infections in 2015). The highest monthly incidence rate occurred in April (n=18; 0.19 per 100,000 persons per year); while the lowest monthly incidence rate occurred in July (n=4; 0.04 per 100,000 persons per year). The median monthly incident rate for 2015 was 0.15 per 100,000 persons per year. The monthly incidence rate for VRE infections did not exceed 0.2 per 100,000 throughout the entire year (data not shown).

VRE Clinical Characteristics

There were 160 prevalent VRE infections identified among all MHS beneficiaries accessing care at an MTF during 2015. A slightly higher percentage of these infections was identified in an inpatient setting (52.5%). The majority were classified as non-invasive (71.3%). By collection site, urine accounted for the largest proportion of infections (60.6%). Respiratory sites accounted for only 1.9% of all infections (Table 4). Approximately half of prevalent infections were identified as *E. faecium* (50.6%), followed by unidentified *Enterococcus spp.*; *E. faecalis* (11.3%) accounted for the lowest proportion of prevalent infections (Table 4).

Table 4. Clinical Characteristics of VRE Prevalence Infections in the MHS, CY 2015

	N = 160	
	Count	**Percentage**
Specimen Collection Location		
Inpatient	84	52.5
Outpatient	76	47.5
Infection Type		
Invasive	46	28.8
Other Non-Invasive	114	71.3
Body Collection Site		
Blood	20	12.5
Respiratory	3	1.9
SSTI/Wound	16	10.0
Urine	97	60.6
Other	24	15.0
Organism Species		
Enterococcus faecalis	18	11.3
Enterococcus faecium	81	50.6
Enterococcus species	61	38.1

Data Source: NMCPHC HL7-formatted CHCS microbiology database.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Exposure Burden Metrics

Table 5 presents two different metrics defining MDRO infection rates for healthcare-associated exposures. During 2015, there were 252,751 inpatient admissions for beneficiaries across all MHS facilities, and the overall MDRO prevalence rate for VRE infections was 0.59 per 1,000 inpatient admissions; this measures the exposure of infection at any point during the admission or one year prior. The US West (0.75 per 1,000 inpatient admissions) and US South (0.68 per 1,000 inpatient admissions) regions had the highest overall MDRO prevalence rates. The admission MDRO prevalence rates were slightly lower than the overall MDRO prevalence rates, at 0.42 per 1,000 inpatient admissions; this measures the magnitude of VRE infection at the time of admission (importation of MDRO into the healthcare system) or one year prior. These results demonstrate that a large proportion of VRE infections are imported into the MHS from the community, because the admissions prevalence metric contributes to the overall prevalence metric. Admission MDRO rates by region were also comparable to overall MDRO rates, with the highest rates exhibited in the US West (0.53 per 1,000 inpatient admissions) and US South (0.49 per 1,000 inpatient admissions) (Table 5).

Table 5. MDRO Healthcare-Associated Exposure Burden Metrics among VRE in the MHS, CY 2015

	Overall MDRO Prevalence[a]		Admission MDRO Prevalence[b]	
	Count	Rate[c]	Count	Rate[c]
Region				
OCONUS	2	--	2	--
US Midwest	2	--	2	--
US Northeast	0	--	0	--
US South	40	0.68	29	0.49
US South Atlantic	45	0.54	31	0.37
US West	61	0.75	43	0.53
Total	150	0.59	107	0.42

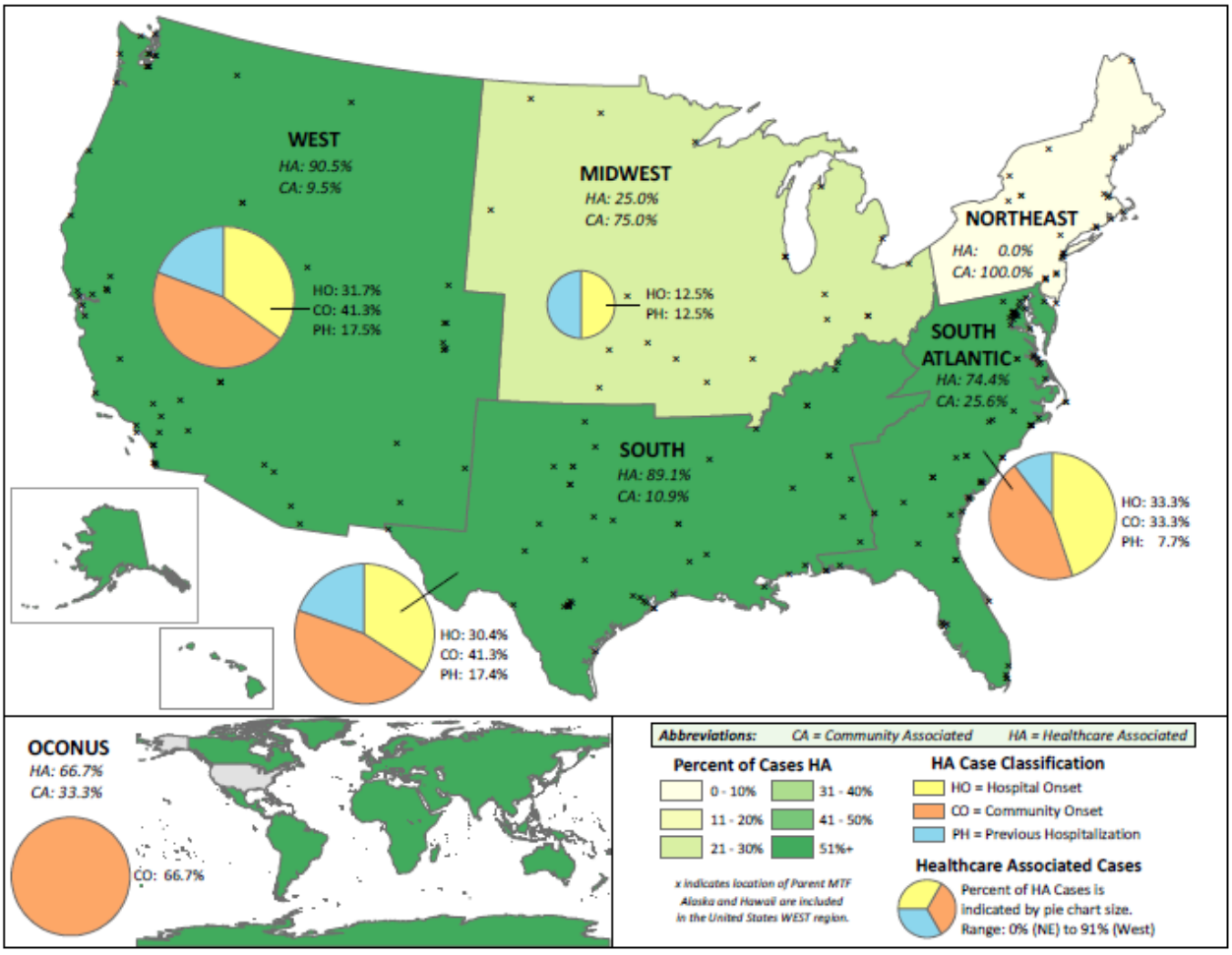
[a] Overall MDRO prevalence included all individuals with an MDRO infection identified from a sample collected at any point during the admission, as well as samples that tested positive for infection in the prior calendar year.
[b] Admission MDRO prevalence included all individuals with an MDRO infection identified from samples collected up to and including the third day of admission, as well as samples that tested positive for infection in the prior calendar year.
[c] Rates are presented as the rate per 1,000 inpatient admissions per year. Rates are not provided when the prevalence count is less than or equal to 5.
Data Source: NMCPHC HL7-formatted CHCS microbiology database.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Epidemiologic Infection Classifications

Among the 160 prevalent VRE infections identified in the MHS during 2015, 18.1% (n=29) were CA cases and 81.9% (n=131) were HA cases. HA cases were further categorized into HO, CO, or previous hospitalization (PH) classifications. Among the 131 prevalent VRE infections identified as HA cases, the largest proportion were identified as CO (45.8%; n=60), indicating that the specimen was collected within the first three days of the hospital admission and the organism was most likely contracted in the community setting. The second largest proportion of HA cases were HO (36.6%; n=48), indicating the specimen was collected after the third day of admission and therefore likely a result of the current hospitalization. A smaller percentage (17.6%; n=23) of all HA cases were PH, indicating the specimens were not associated with a current admission but the patient had a prior hospitalization in the previous 12 months (data not shown).

Regionally, the West reported the highest proportion of HA VRE cases (90.5%), followed by the South (89.1%) and South Atlantic (74.4%). CO cases represent the largest percentage of HA cases in the West (41.3%) and South (41.3%), whereas the percentage of HA cases in the South Atlantic are evenly distributed between CO (33.3%) and HO (33.3%) cases. Smaller frequencies of prevalent VRE infections were identified in the Midwest (n=8), Northeast (n=1) and OCONUS locations (n=3). The majority of these infections in the Midwest were CA cases (n=6; 75%) as opposed to HA cases (n=2; 25%), with the percentage of HA cases evenly split between HO (n=1; 12.5%) and PH (n=1; 12.5%). Of the three prevalent infections identified OCONUS, two were classified as HA cases (66.7%), both of which were CO. The one prevalent VRE infection identified in the Northeast was classified as a CA case (Figure 2).

Figure 2. Proportion of Healthcare- and Community-Associated Cases among VRE Infections in the MHS by Region, CY 2015



Data Source: NMCPHC HL7-formatted CHCS microbiology, SIDR, and MHS M2 databases.
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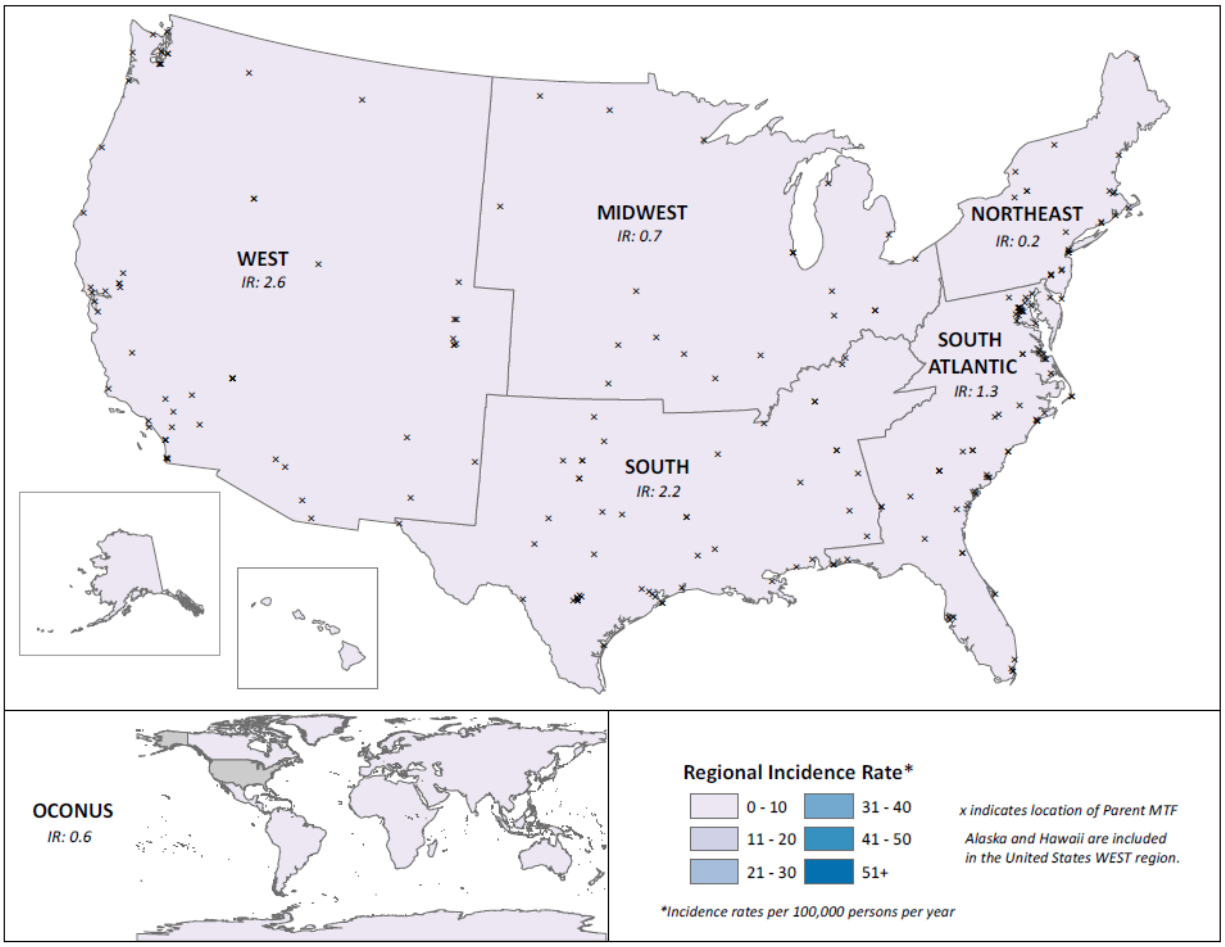
Section B – Antimicrobial Resistance and Use

Regional Multidrug Resistance

The 2015 annual incidence rate of VRE among all MHS beneficiaries was 1.60 per 100,000 persons per year. Regionally, the highest incidence rates occurred in the West (2.57 per 100,000 persons) and South (2.15 per 100,000 persons), and the lowest rates were in OCONUS locations (0.57 per 100,000 persons) and the Northeast (0.16 per 100,000 persons) (Figure 3).

Figure 3. Annual Incidence Rate (IR) among VRE Infections in the MHS by Region, CY 2015



Rates are presented as the rate per 100,000 persons per year.
Data Source: NMCPHC HL7-formatted CHCS microbiology, SIDR, and MHS M2 databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Antibiogram

Table 6 displays an antibiogram of VRE infections for all MHS beneficiaries from 2010 through 2015. In 2015, VRE infections were more than 95% susceptible to linezolid (95.2%) and daptomycin (98.0%). Tetracycline (8.2%) and ciprofloxacin (15.8%) demonstrated the lowest levels of efficacy. During 2010 to 2015, statistically significant increasing trends in efficacy were observed for ampicillin, ciprofloxacin, gentamicin high level, linezolid, and penicillin. Tetracycline was the only antibiotic to which VRE infections demonstrated a statistically significant decreasing trend in susceptibility during the same time period (Table 6).

Table 6. Antibiogram of VRE Infections Identified in the MHS, CY 2010-2015

	2010	2011	2012	2013	2014	2015	Susceptibility Trend	Comment[a]
Ampicillin	17.2	13.1	18.3	24.7	29.3	21.2		↑
Ciprofloxacin	5.7	7.3	2.0	13.6	8.3	15.8		↑
Daptomycin	--	--	--	--	92.7	98.0		
Doxycycline	--	--	--	--	--	--		
Erythromycin	--	--	--	--	--	--		
Gentamicin High Level	61.6	61.8	73.0	84.5	82.5	86.6		↑
Levofloxacin	5.1	10.8	--	25.0	8.3	20.0		
Linezolid	82.8	87.2	92.9	97.4	87.5	95.2		↑
Nitrofurantoin	34.8	32.7	35.2	50.9	50.0	36.8		
Penicillin	13.0	12.2	9.2	28.8	24.0	16.7		↑
Quinupristin/ Dalfopristin	78.3	--	86.7	--	--	--		
Rifampin	--	--	--	--	--	--		
Streptomycin High Level	61.0	66.7	69.5	77.8	69.4	68.2		
Tetracycline	33.0	27.4	14.1	16.0	18.3	8.2		↓

'--' indicates that fewer than 30 isolates were tested.

[a] Arrow indicates the antibiotics with a significant change in direction of trend for significant two-tailed Cochrane-Armitage tests for trend established for a single antibiotic over time. A significant increase in susceptibility is denoted by a green upward arrow and a significant decrease in susceptibility is denoted by a blue downward arrow.

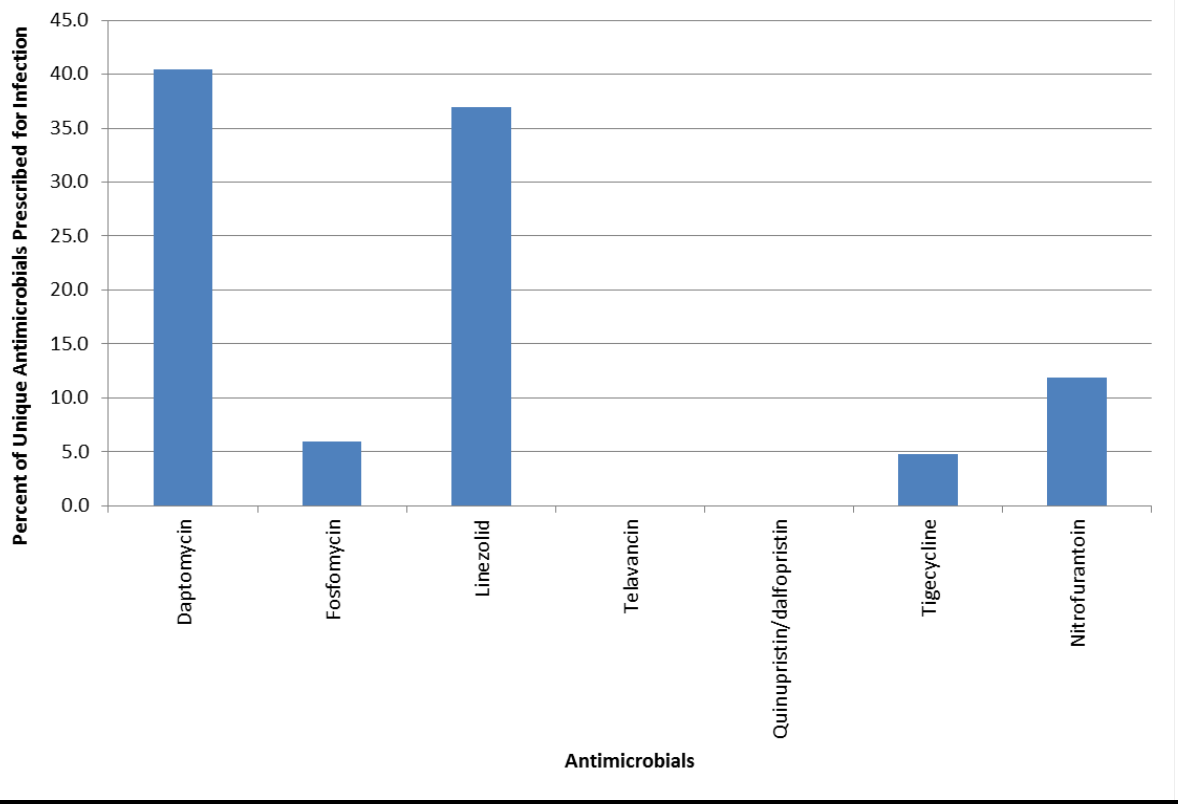
Data Source: NMCPHC HL7-formatted CHCS microbiology database.

Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Antimicrobial Consumption/Prescription Practices

Figure 4 displays the percentage of unique antimicrobials prescribed for prevalent VRE infections during 2015, including seven antibiotic classes recommended for VRE treatment according to the Johns Hopkins Antibiotic Guide.[22] A total of 84 unique prescriptions were provided within the seven recommended antibiotic classes. The most commonly prescribed antimicrobials included daptomycin (n=34; 40.5%), linezolid (n=31; 36.9%), and nitrofurantoin (n=10; 11.9%). No prescriptions for telavancin or quinupristin/dalfopristin were identified in 2015 (Figure 4).

Figure 4. VRE Infection and Prescription Practices in the MHS, CY 2015



Only the first occurrence of a unique antibiotic was counted per person per infection, regardless of administration route.
Data Source: NMCPHC HL7-formatted CHCS microbiology and HL7-formatted pharmacy databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Section C – Special Populations

There were no deployment-related VRE infections among DON active duty personnel during CY 2015.

Discussion

This analysis found an increase in VRE infection rates in recent years, though minimal, from the historic baseline of 1.34 infections per 100,000 persons to 1.60 infections per 100,000 persons in 2015. While this increase may be influenced by the use of new processing software with potential to enhance data capture in the MHS, recent studies indicate VRE infections are also rising in general populations in the US and abroad. One US study reported hospitalizations due to VRE infections increased from 3.2 per 10,000 hospitalizations to 6.5 per 10,000 total hospitalizations from 2003-2006.[10] A meta-analysis of VRE incidence rates in the US between 2000 and 2015 found that rates associated with pooled national data did not increase, but studies from Atlanta and Detroit demonstrated increasing VRE infection rates.[24] A recent study from Europe also demonstrated significant regional differences for VRE, finding that increasing rates among intensive care units were primarily isolated to a belt of four states in the middle of Germany between 2001 and 2011.[25]

Demographic analyses from this study of MHS beneficiaries found the highest VRE rates among males, people aged 65 years and older, and retirees. In comparison to analyses defining clinical characteristics, the demographic results by gender were unexpected, as the majority of the infections originated from urine specimens. Females are typically more prone to UTIs than males, and previous assessments among DOD beneficiaries reported relatively equal VRE infection rates between males and females.[26,27] Results by age distribution were expected, because older persons are more likely to become ill and experience hospitalizations, where many of VRE infections are acquired.[28]

Geographic analyses indicated that the regions with the highest overall VRE rates, including US West, US South, and US South Atlantic, also demonstrated the largest proportions of HA cases. In contrast, the US Midwest and US Northeast regions demonstrated the lowest VRE rates with larger proportions of CA cases. In the US, surveillance for VRE primarily originates within hospital settings, and little research suggests that transmission among healthy adults occurs at a significant extent in the community.[2] However, as colonized patients leave the hospital environment, the possibility for transmission into the community cannot be disregarded. Research demonstrates that patients can remain colonized for weeks to months and are often still colonized at the time of readmission to the hospital.[29] Results from this analysis support the potential for community transmission from the hospital environment, as the largest percentage of HA cases within the US West and US South regions were classified as CO. Although the total frequency of VRE infections identified in the US Midwest and US Northeast regions was low, the larger proportion of these infections classified as CA cases may also support the potential for community transmission.

This report presents two different metrics defining MDRO infection rates for healthcare-associated exposures by region; the admissions prevalence metric measures the magnitude of VRE imported into the healthcare system, and the overall prevalence rate measures the reservoir of infection in a healthcare setting.[21] Less than five laboratory results fitting the overall or admission prevalence definition were identified in OCONUS, US Midwest, and US Northeast regions, thus rates were either suppressed or equal to zero. In the US West, US South, and US

South Atlantic, each region demonstrated a slightly higher overall prevalence rate than the admissions prevalence rate. Because the admissions prevalence metric contributes to the overall prevalence metric, these results feasibly demonstrate that a large proportion of VRE infections are imported into the MHS; the admissions prevalence rate during 2015 (0.42 per 1,000 inpatient admissions) accounted for approximately two-thirds of the overall prevalence metric (0.59 per 1,000 inpatient admissions). These results further support discussion around the growing potential for community transmission as opposed to transmission within the hospital setting.

Treatment for infections due to VRE, particularly *E. faecium*, may pose serious challenges due to resistance against multiple antibiotics; however, VRE infections still maintain susceptibility to some antibiotics.[2,22] VRE infections in the MHS remained most susceptible to daptomycin and linezolid over the surveillance period and surpassed 95% susceptibility to both drugs in 2015. While daptomycin did not demonstrate any significant trend in efficacy, VRE susceptibility to linezolid maintained a statistically significant increase. Gentamycin demonstrated the most noteworthy, significant increase in efficacy; VRE susceptibility to gentamycin increased from 61.6% in 2010 to 86.6% in 2015. Only one antibiotic, tetracycline, demonstrated a significant decrease in efficacy.

Daptomycin and linezolid were the most commonly prescribed antimicrobials for VRE infections during 2015, which is consistent with treatment recommendations from the Johns Hopkins Antibiotic Treatment Guide, as well as MHS microbiology results confirming high susceptibilities for these two antibiotic classes.[22] Daptomycin remains the only antibiotic with in vitro bactericidal activity against VRE that is approved by the US Food and Drug Administration (FDA). Researchers caution clinicians to be aware of the potential emergence of daptomycin non-susceptible enterococci strains, particularly with the treatment of bloodstream infections, as data for this susceptibility remains limited.[22,30] The Johns Hopkins Antibiotic Guide recommends evaluating the susceptibility of isolates to monitor minimum inhibitory concentrations of sequential isolates recovered during daptomycin treatment.[22] Although this analysis of the MHS did not assess whether or not each VRE infection receiving a prescription for daptomycin also had susceptibility testing, the results do indicate the number of laboratory results for daptomycin susceptibility testing exceeded the number of unique prescriptions for this antibiotic.

The National Healthcare Safety Network (NHSN) report for 2006-2007 identified VRE and MRSA as the two most common antimicrobial-resistant pathogens associated with healthcare-associated infections.[31] Experts note the widespread use of vancomycin to treat MRSA likely contributes to the emergence, continued spread, and increasing trend of VRE infections in the US.[12,25] In 1975, MRSA prevalence in ICU patients within US hospitals was estimated at 2.4% and increased to 59.5% by 2003. During this same time period, the estimated percentage of VRE infections among ICU patients also trended upward, increasing to 28% in 2003.[12] One study describes a prevalence for VRE-MRSA colonization or coinfection among patients in a tertiary-care facility at 19.8%, with significant risk factors including isolation of vancomycin-resistant *E. faecalis* and the use of linezolid or clindamycin.[32] The risk factors and epidemiology of colonization or coinfection with both VRE and MRSA have yet to be described in DOD populations, which merits consideration for future studies.

In summary, upward trends in VRE infection rates among beneficiaries seeking care within the MHS are consistent with other literature supporting recent rises in VRE infections, with a particular focus on elevated rates by region. The US West and US South regions accounted for the largest incidence rates during 2015, and cases were primarily characterized as HA. While the majority of VRE surveillance within the US originates from hospital settings, these results indicate a need to evaluate the potential for community transmission of VRE. This is demonstrated by the substantial percentage of HA cases classified as CO, as well as elevated MDRO admission metrics, which indicate a higher magnitude of VRE is imported into the healthcare system rather than preexisting as a reservoir. Finally, these results indicate viable treatment options are still available for VRE infections in the MHS and that prescribing practices are supported by susceptibility testing trends.

Limitations

HL7-formatted data are generated within the CHCS at fixed MTFs; therefore, this analysis does not include microbiology records from purchased care providers, shipboard facilities, battalion aid stations, or in-theater facilities.

Microbiology data are useful for identifying laboratory-confirmed infections. However, infections that were treated presumptively without laboratory confirmation do not exist in the microbiology data. Clinical practice with regards to culturing varies between providers and facilities. Examples of situations where cultures may not be performed include confirmatory tests for patients with influenza-like illness (ILI) symptoms, or patients with superficial infections who are treated presumptively. Therefore, infection counts identified here may be an underestimate of the actual burden of VRE in the MHS.

The data restructuring process for the analysis of clinical characteristics and antimicrobial resistance does not capture non-standard CHCS records. These non-standard records may include those containing the results of tests performed at reference laboratories or novel organism antibiotic combinations. The use of microbiology data for analysis of antibiotic resistance is also limited by the practice of cascade reporting, in which antibiotic sensitivity results are conditionally reported in CHCS to guide antimicrobial selection and treatment decisions. Cascade reporting is practiced to varying degrees at MHS MTFs.

The EDC data feed does not include records on medical encounters conducted outside the MHS (e.g., purchased care in the community) and it cannot be determined if an individual truly had no healthcare contact or other risk factors for VRE infection, or if the individual had a risk factor that was not visible in the available data. Data on other factors commonly used to define HA infections were not available (e.g., presence of an invasive device, history of dialysis or surgery, a long-term care facility stay in the 12 months preceding the culture). Therefore, there may be HA infections currently miscategorized as CA infections. Without the ability to identify these HA infections, a more accurate estimate of CA infections could not be determined. Given the relatively healthy military population, however, any misclassification bias is likely minimal.

The pharmacy databases consist of outpatient non-intravenous prescriptions (outpatient), inpatient non-intravenous prescriptions (unit dose), and intravenous prescriptions (intravenous). Though treatment compliance in the inpatient setting can be assumed, outpatient pharmacy records indicate that a patient received a prescription and subsequent compliance is unknown. Due to near real-time data feeds, analysts are able to determine if a prescription was edited or canceled; however, the time difference between these events may allow for a short period of treatment not considered in this analysis. During ongoing surveillance efforts, patient treatment status may change as edited or canceled prescription records are received.

It is possible that not all antibiotic prescriptions were dispensed in response to a VRE infection. Antibiotics that were prescribed within the appropriate timeframe to be associated with a VRE specimen collection date may have actually been provided for reasons other than the documented infection, such as a different infection occurring after VRE was isolated. However, most

antibiotics identified as being associated with a VRE infection were antibiotics that are typically used to treat VRE, so it is likely that the majority of prescriptions in this analysis were truly in response to the VRE infection.

DMDC provides monthly snapshots of each active duty, reserve, and deployed Navy and Marine Corps service member's personnel record. Data are provided to DMDC by the service and analyses are dependent on the quality and completeness of these data. Any changes in service member status after the monthly data are extracted will not be captured until the following month. Active duty and reserve personnel records are maintained in separate databases, but activated reservists may be captured in the active duty DMDC file rather than the reserve DMDC file. Unit Identification Codes (UICs) reported for Marine Corps service members represent Reporting Unit Codes (RUCs), rather than UICs.

Personnel records for deployed service members are provided via CTS. The purpose of DMDC CTS is to capture personnel information for Central Command (CENTCOM) deployments. Additionally, deployment start and end dates are derived from the following systems and may not reflect the actual dates of deployment: Defense Finance Accounting System (DFAS), the Deployed Theater Accountability System (DTAS), the Secure Personnel Accountability System (SPA), historical PERSTEMPO files, and the Individual Personnel TEMPO Program. A country location of ZZ may represent shipboard or an unknown deployment location.

Infections may not be uniformly distributed within a spatial region; no distinctions were made with regard to the heterogeneity of incidence rates or prevalence among subunits (e.g., states, non-US countries). The choropleth maps represent an annual snapshot of infections and do not reflect the geographic movement of service members within the course of a year. Infections were georeferenced according to the locations of the MTFs where they were encountered, not according to the deployment locations or home locations of the service members. Map area does not equate to population size; parent MTF locations are displayed within US regions to convey the density of military medical facilities within each region.

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Appendix A: Acronym and Abbreviation List

Acronym/Abbreviation	Definition
AD	active duty
BSI	bloodstream infection
CA	community-associated
CDC	Centers for Disease Control and Prevention
CENTCOM	Central Command
CHCS	Composite Health Care System
CLSI	Clinical and Laboratory Standards Institute
CO	community-onset
CONUS	continental United States
CTS	Contingency Tracking System
CY	calendar year
DFAS	Defense Finance Accounting System
DMDC	Defense Manpower Data Center
DOD	Department of Defense
DON	Department of the Navy
DTAS	Deployed Theater Accountability System
EDC	EpiData Center Department
FDA	Food and Drug Administration
HA	healthcare-associated
HAI	healthcare-associated infection
HICPAC	Hospital Infection Control Practices Advisory Committee
HL7	Health Level 7 format
HO	hospital-onset
ICU	intensive care unit
ILI	influenza-like illness
IR	incidence rate
IV	intravenous
M2	Military Health System (MHS) Management Analysis and Reporting Tool
MDR	multidrug-resistant
MDRO	multidrug-resistant organism
MEPRS	Medical Expense and Performance Reporting System
MHS	Military Health System
MRSA	methicillin-resistant *Staphylococcus aureus*
MTF	military treatment facility
NMCPHC	Navy and Marine Corps Public Health Center
OCONUS	outside the continental United States
OP	outpatient
PDR	pandrug-resistant
PH	previous hospitalization
RUC	reporting unit code
SHEA	Society for Healthcare Epidemiology of America
SIDR	Standard Inpatient Data Record
SPA	Secure Personnel Accountability System
SSTI	skin and soft tissue infection

Acronym/Abbreviation	Definition
UD	unit dose
UIC	unit identification code
US	United States
UTI	urinary tract infection
VRE	vancomycin-resistant *Enterococcus*
WHO	World Health Organization